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Safety of partial selective COX-2 inhibitors in patients with cross-reactive NSAID hypersensitivity and factors affecting safety

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ABSTRACT

Aims: Partial selective COX-2 inhibitors, such as nimesulide, or meloxicam are tolerated by the majority of the patients with cross-reactive NSAID hypersensitivity. This study aimed to obtain more information about the safety of partial selective COX-2 inhibitors; nimesulide and meloxicam in non-immunologic type, cross-reactive NSAID hypersensitivity and to detect risk factors for intolerance to these drugs.

Methods: This is a retrospective study of patients with suggestive of cross-reactive NSAID hypersensitivity who admitted to our clinic over a period of 10 years. Patients who had a reliable history of immediate type NSAIDs hypersensitivity with at least 2 chemically unrelated class and/or positive ASA provocation test and who underwent alternative drug provocation test with partial selective COX-2 inhibitors (nimesulide and/or meloxicam) were included to study. Patients' demographics, comorbidities, atopy status, duration of NSAID hypersensitivity, total number of reactions, reaction grades, clinical phenotypes, pulmonary function test parameters and results of alternative drug provocation test results are recorded. Patients with and without reactions during alternative provocation tests with nimesulide and/or meloxicam were compared in terms of these data.

Results: A total of 560 patients were included in the study, 378 (67.5%) of them were female. Allergic comorbidities were detected in 394 (72.6%) patients. Asthma, other drug allergies and nasal polyp were the most common comorbidities. Alternative drug provocation test positivity with nimesulide and/or meloxicam was detected in 50 of 560 (8.9%) patients. Provocation test positivity was 33/541 (6.1%) with nimesulide, 30/517 (5.8%) with meloxicam and 13/498 (2.3%) with both nimesulide and meloxicam. Duration of NSAID hypersensitivity was shorter and allergic comorbidities, asthma, nasal polyp and the coexistence of asthma and nasal polyp were more common in patients with a positive provocation test.

Conclusion: The partial selective COX-2 inhibitors nimesulide and meloxicam are well tolerated alternatives in patients with cross-reactive NSAID hypersensitivity. Hypersensitivity to these drugs is significantly higher in patients with asthma and/or nasal polyp than other group of cross-reactive NSAID hypersensitive patients and also in patients with a shorter duration of NSAID hypersensitivity.

Keywords: NSAID, hypersensitivity, COX-2 inhibitor, nimesulide, meloxicam, safety

Our study has been presented previously as an poster presentation in XXVI. Ulusal Alerji ve Klinik İmmünoloji Kongresi (poster number P-130) (2019).

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most frequently prescribed medicines worldwide and they are the drugs most commonly involved in drug hypersensitivity reactions (DHRs).[1-3]

The NSAID-induced hypersensitivity reactions involve different mechanisms and current classification is based on these mechanisms as allergic (immunologic) or nonspecific pharmacologic (non-immunologic) mechanisms. Non-immunologically mediated or cross-reactive NSAID hypersensitvity involves NSAIDs-exacerbated respiratory disease (NERD), NSAIDs-exacerbated cutaneous disease (NECD) and multiple NSAIDs-induced urticaria/angioedema (NIUA).[1-3]

Underlying mechanism is important for the management of patients with NSAID hypersensitivity. The mechanism of non-immunologic hypersensitivity is related to cyclooxygenase-1 (COX-1) inhibition. COX is an enzyme that metabolizes arachidonic acid to prostaglandins, thromboxanes and prostacyclin. Inhibition of COX-1 by NSAIDs may lead to a decrease in protective prostaglandins production which is normally act as a brake on the production of cysteinyl leukotrienes and lead to activation of mediator release from inflammatory cells such as mast cells and eosinophils.[1-5]

In case of a history of reactions with more than one chemically unrelated COX-1 inhibitor, the cross-reactive type can be suspected and the mechanism of the reaction is not immunological.[2]

NSAIDs have different chemical structures that share the capacity for inhibiting COX enzymes (COX-1 and COX-2). According to the 'COX' hypothesis, inhibition

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of COX-1 (but not COX-2) by asetyl salicylic acid (ASA) or other NSAIDs triggers mechanisms leading to symptoms[3,6] NSAIDs that are strong COX-1 inhibitors induce reactions in patients with cross-reactive NSAID hypersensitivity and should be avoided in these patients. Weak COX-1 inhibitors (e.g acetaminofen) in low doses or selective COX-2 inhibitors are generally well tolerated.[2-4] Partial selective COX-2 inhibitors, such as nimesulide, or meloxicam are tolerated by the majority of the patients and may be used as safe alternative analgesic drugs if tolerated on the provocation tests.[7]

Most of the previous studies evaluating the safety of partial selective COX-2 inhibitors in NSAID hypersensitivity have been done before the current classification and that do not fully account for cross-reactivity. The aim of this study was to obtain more information about the safety of partial selective COX-2 inhibitors; nimesulide and meloxicam in non-imunologic type, cross-reactive NSAID hypersensitivity and to detect risk factors for intolerance to these drugs.

METHODS

Ethics

This is a retrospective study of patients with suggestive of cross-reactive NSAID hypersensitivity who admitted to our clinic over a period of 10 years; between January 2009 and January 2019. The study was approved by local ethics committee (Date: 12.10.2021, Decision No: 2012-KAEK-15/2373). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion Criterias

A total of 1140 patient data reviewed. A total of 560 patients who had a reliable history of immediate type NSAIDs hypersensitivity with at least 2 chemically unrelated class and/or positive ASA provocation test (n=27) and who underwent alternative drug provocation test with partial selective COX-2 inhibitors (nimesulide and/or meloxicam) were included to study.

NSAIDs hypersensitivity is characterized by the development of any symptoms including urticaria, angioedema, bronchospasm, nasoocular symptoms or anaphylaxis induced by at least two NSAIDs with different chemical groups.

Exclusion Criterias

A total of 580 patients who had delayed type NSAID hypersensitivity (n:34), negative ASA provocation test (n=235), only one reaction history (n=174), more than one reaction but within the same chemical class (n=48), unreliable history (n=71), unavailable records (n=18) were excluded from study.

Patient Characteristics

Patients' demographics, concomitant diseases, atopy status, duration of NSAID hypersensitivity, total number of reactions, reaction severities, clinical phenotypes, pulmonary function test (PFT) parameters and results of alternative drug provocation test results are recorded. Patients with and without reactions during alternative provocation tests with nimesulide and/or meloxicam were compared in terms of these data.

Presence of atopy was defined by measurement of allergen spesific IgE or skin prick test (SPT) positivity to at least one of the following aeroallergens; Dermatophagides pteronyssinus (der p); Dermatophagoides farinae (der f); cockroach; grass, tree, weed pollens; cat; dog; Alternaria; Cladosporium and Aspergillus antigens. Positive (histamine, 10 mg/mL) and negative (saline solution) controls were included. SPT was considered positive when the skin reaction was a wheal at least 3mm diameter greater than control solution with a surrounding erythema. An allergen-specific IgE level >0.35 kU/L was accepted as positive.

Drug Provocation Tests

Single blinded, placebo-controlled, oral, drug provocation tests with partial selective COX-2 inhibitors (nimesulide and/or meloxicam) were performed to assess the tolerance to these drugs. All patients gave an informed written consent before each challenge session.

On the first day divided doses of one-quarter and three-quarters placebo tablets (lactose) were given at 1 hour intervals. If the placebo challenge was negative divided doses of one-quarter and three-quarters of the therapeutic doses of nimesulide and/or meloxicam were given at 1 hour intervals on different days. Total challenge doses were 100 mg for nimesulide and 7.5 mg for meloxicam.

All drug challenges were performed under close observation of patient in the allergy unit. Emergency equipment was available during all challenges. Patients were observed at hospital for at least two hours after last dose administration and were seen in the outpatient department on the next day to determine whether any delayed reactions had occurred.

All patients were challenged at least 4 weeks after their most recent adverse reaction. None of the patients presented significant cutaneous or respiratory symptoms at the time of testing, Patients with chronic urticaria were challenged during a period of clinical remission of the disease. Antihistamines had been discontinued seven days or more before challenges.

During the challenge procedure blood pressure, pulse, nasoocular, respiratory and cutaneous symptoms were monitored before and every hour after each dose was given. Forced expiratory volume in 1 second (FEV1) was measured before each dose and any time if respiratory symptoms occurred.

Challenge test was accepted as positive if one of the following symptoms existed: conjunctival reaction; the upper and lower respiratory tract reactions such as sneezing, rhinorrhea, nasal blockage, dyspnea, wheezing, and cough with a 20% decrease in FEV1; cutaneous reactions such as erythema, pruritus with erythema, urticaria, angioedema; hypotension and/or anaphylactoid reaction.

The severity of culprit and alternative drug hypersensitivity reactions were classified according to Ring and Messmer Classification.[8]

Statistical Analysis

All statistical analyses were performed using the SPSS (statistical package of social sciences) for Windows 18,0 software package. In the evaluation of the data, mean and standard deviation for normally distributed variables, median and interquartile range for non-normally distributed variables, values and percentages for ratios were determined by descriptive statistical method. In univariate analyses, Chi-square, Fischer, Student's t-test and Mann-Whitney U tests were used, as appropriate. All p values lower than 0.05 were considered to be statistically significant.

RESULTS

A total of 560 patients; 378 (67.5%) female and 182 (32.5%) male with mean age 43±13.29 were included to study.

Median duration of NSAID hypersensitivity was 36 (1-420) months. 184 patients had two, 376 patients had three or more reactions. The highest reaction grades with culprit NSAIDs were grade 1 in 197 (35.2%), grade 2 in 162 (28.9%), grade 3 in 200 (35.7%), grade 4 in 1 (0.2%) patients.

Atopy was detected in 141 of 449 (31.4%) patients; 52 (36.9%) had polysensitization and 89 (63.1%) had monosensitization.

In the evaluation of comorbidities, non-allergic comorbidities were detected in 198 (36.9%) patients and allergic comorbidities were detected in 394 (72.6%) patients. Allergic comorbidities were shown in **Table 1**. Asthma, other drug allergies and nasal polyp were the most common comorbidities. Median duration of asthma and nasal polyp was 48 (0-480) months and 36 (0-240) months respectively. Seventy-two patients (68.6%) had a history of nasal polyp operation with median 2 (1-10) operations.

None of the patients experienced any reaction to placebo challenge. Alternative drug provocation test was performed with nimesulide in 541 patients, meloxicam in 517 patients, both nimesulide and meloxicam in 498 patients. Alternative drug provocation test positivity with nimesulide and/or meloxicam was detected 50 of 560 (8.9%) patients. Provocation test positivity was 33/541 (6.1%) with nimesulide, 30/517 (5.8%) with meloxicam and 13/498 (2.3%) with both nimesulide and meloxicam.

Table 1. Allergic comorbidities of study group

Allergic comorbidity	n (%)
Asthma	199 (36.9)
Other drug allergy	159 (29.3)
Nasal polyp	123 (22.8)
Asthma+nasal polyp	106 (18.9)
Allergic rhinitis	100 (18.6)
Chronic urticaria / angioedema	90 (16.7)
Non-allergic rhinitis	13 (2.4)
Venom allergy	18 (3.4)
Food allergy	12 (2.2)
Contact dermatitis	5 (0.9)
Atopic dermatitis	2 (0.4)
Latex allergy	2 (0.4)
Idiopathic anaphylaxis	1 (0.2)

Most of the reactions occurred after full therapeutic dose administration; 25/33 (75.8%) of nimesulide and 26/30 (86.7%) of meloxicam reactions. The characteristics of reactions with nimesulide and meloxicam are shown in **Table 2**. No significant difference was detected in terms of provocation test positivity ratio, reaction severity, provocative dose, interval between the last administered drug dose and reaction and clinical symptoms (**Table 2**).

Table 2. The characteristics of reactions with nimesulide and meloxicam

Reaction Properties	Nimesulide n (%)	Meloxicam n (%)	p
Provocation test positivity	33 (6.1)	30 (5.8)	0.838
Reaction severity			0.244
Grade 1	13 (39.4)	16 (53.3)	
Grade 2	7 (21.2)	8 (26.7)	
Grade 3	13 (39.4)	6 (20)	
Provacative dose			0.271
One quarter tablet	8 (24.2)	4 (13.3)	
Three quarters tablet	25 (75.8)	26 (86.7)	
Interval between last drug dose and reaction			0.405
<1 hour	10 (30.3)	7 (23.3)	
1-2 hours	12 (36.4)	8 (26.7)	
>2 hours	11 (33.3)	15 (50)	
Clinical symptoms			
Pruritus with erythema	13 (39.4)	12 (40)	0.964
Urticaria	10 (30.3)	11 (36.7)	0.593
Angioedema	6 (18.2)	6 (20)	0.854
Dyspnea	14 (42.4)	7 (23.3)	0.108
Bronchospasm	13 (39.4)	6 (20)	0.094
Rhinitis	10 (30.3)	10 (33.3)	0.796
Conjunctivitis	2 (6.1)	2 (6.7)	1.000
Nausea	1 (3)	3 (10)	1.000
Vomiting	1 (3)	1 (3.3)	1.000
Difficulty swallowing	2 (6.1)	2 (6.7)	1.000
Hypotension	2 (6.1)	-	0.494
Tachycardia	2 (6.1)	-	0.494
Dizziness	1 (3)	3 (10)	1.000
Hypertension	1 (3)	1 (3.3)	1.000
Tremor	1 (3)	-	1.000
Buzzing in the ear	3 (9.1)	-	0.240

Comparision of patients with positive (n:50) or negative (n:510) drug provocation test with nimesulide and/or meloxicam revealed that duration of NSAID hypersensitivity was shorter and allergic comorbidities, asthma, nasal polyp and the coexistence of asthma and nasal polyp were more common in patients with a positive provocation test (Table 3).

No significant difference was detected in alternative drug provocation test positivity in asthma patients according to PFT parameters (Table 4).

Table 4. Pulmonary function test parameters of asthma patients according to drug provocation test results

Variables	Positive DPT (n=173)	Negative DPT (n=26)	p
FVC (%)	92.72±14.79	95.20±14.74	0.439
FEV1 (%)	88.48±15.86	88.64±10.21	0.947
FEV1 (ml) median (min-max)	2410 (740-5200)	2680 (1640-4010)	0.242
FEV1/FVC	83 (50-94)	83 (56-91)	0.381
MMFR	75.05±24.10	69.36±20.87	0.270

DPT: Drug provocation test, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capasity, MMFR: Maximum mid flow rate

Table 3. Comparision of the patients with positive or negative drug provocation test with nimesulide and/or meloxicam

Variables	All patients (n=560)	Patients with negative DPT (n=510)	Patients with positive DPT (n=50)	p
Age (years)	43.00±13.29	43.29±13.37	40.40±12.30	0.143
Gender Female, n (%) Male, n (%)	 378 (67.5) 182 (32.5)	 343 (67.3) 167 (32.7)	 35 (70) 15 (30)	 0.692
Atopy, n (%)	141 (31.4)	127 (31.2)	14 (33.3)	0.777
NSAID hypersensitivity duration, months median (min-max)	36 (1-420)	36 (1-420)	18 (1-180)	0.017
NSAID reaction number 2 ≥3	 184 (32.9) 376 (67.1)	 170 (33.3) 340 (66.7)	 14 (28.0) 36 (72.0)	 0.444
NSAID reaction severity Grade 1 Grade 2 Grade 3 Grade 4	 197 (35.1) 162 (28.9) 200 (35.7) 1 (0.2)	 183 (35.9) 143 (28.0) 183 (35.9) 1 (0.2)	 14 (28.0) 19 (38.0) 17 (34.0) 0 (0.0)	 0.474
Non-allergic comorbidity, n (%)	198 (36.9)	179 (36.8)	19 (38)	0.870
Allergic comorbidity, n (%)	394 (72.6)	349 (88.6)	45 (90.0)	0.004
Asthma, n (%)	199 (36.9)	173 (35.4)	26 (52.0)	0.020
Nasal polyp, n (%)	123 (22.8)	102 (20.8)	21 (42.0)	0.001
Asthma and nasal polyp, n (%)	106 (18.9)	87 (17.1)	19 (38.0)	<0.001
Other drug allergy	159 (29.3)	143 (29.0)	16 (32.0)	0.553
Chronic urticaria / angioedema	90 (16.7)	81 (16.6)	9 (18.0)	0.800
Allergic rhinitis	100 (18.6)	90 (18.5)	10 (20.0)	0.793
Non-allergic rhinitiis	13 (2.4)	11 (2.3)	2 (4.0)	0.345
Venom allergy	18 (3.4)	16 (3.3)	2 (4.0)	0.680
Food allergy	12 (2.2)	12 (2.4)	0 (0.0)	0.613
Asthma duration, months median (min-max)	48 (0-480)	54 (0-480)	48 (0-240)	0.608
Nasal polyp duration,months, median(min-max)	36 (0-240)	48 (0-240)	24 (0-240)	0.259
Presence of polyp operation n (%)	72 (68.6)	59 (69.4)	13 (65.0)	0.702
Polyp operation number median (min-max)	2 (1-10)	2 (1-10)	1.5 (1-3)	0.062
Asthma and nasal polyp coexistence Respiratory symptoms, n (%) Systemic symptoms, n (%)	 56 (54.4) 47 (45.6)	 47 (56.0) 37 (44.0)	 9 (47.4) 10 (52.6)	 0.498
Underlying chronic urticaria Urticarial exacerbation, n (%) Systemic symptoms, n (%)	 60 (65.9) 30 (33.3)	 54 (65.9) 27 (33.3)	 6 (66.7) 3 (33.3)	 1.000

DPT: Drug provocation test, NSAID: Nonsteroidal anti-inflammatory drug

Drug provocation tests with both nimesulide and meloxicam were performed in 498 patients. Of these patients 29 had positivity with one drug and 13 had positivity with both drugs. No statistically significant difference was observed between cases with positive provocation tests with one or both drugs (Table 5).

Asthma and nasal polyp coexistence were observed in 106 patients. Of these patients 56 (52.8%) had only respiratory symptoms with culprit NSAIDs and 47 (44.3%) had systemic symptoms in addition to respiratory symptoms. No respiratory symptoms was observed in 3 (2.8%) patients with culprit NSAIDs. Median number of previous nasal polyp surgeries was found to be higher in patients who had systemic symptoms than in patients who had only respiratory symptoms; 2 (1-6) vs 1 (1-4) respectively (p=0.013).

Underlying chronic urticaria was present in 90 patients. Of these patients 60 (66.7%) had exacerbation of urticaria with NSAIDs, however 30 (33.3%) had systemic symptoms in adition to urticarial exacerbation after NSAID intake. Allergic rhinitis was more common in patients with urticaria and systemic symptoms than in patients with only urticarial exacerbation; 9 of 30 (31%) vs 6 of 60 (10%) respectively (p=0.018).

No statistically significant difference was detected in alternative drug provocation test positivity in NERD and NECD patients depending on whether there was a systemic response to NSAIDs or not (Table 3 and Table 5).

DISCUSSION

This study, which includes data from a large patient population, demonstrated that nimesulide and meloxicam are well tolerated alternatives in patients with cross-reactive NSAID hypersensitivity. Provocation test positivities with nimesulide and meloxicam were 6.1% and 5.8% respectively.

Table 5. Characteristics of patients with single or double positivity on nimesulide and meloxicam provocation test

Variables	Single positivity (n=29)	Double positivity (n=13)	p
Age (years)	41.48±12.45	36.62±9.57	0.219
Gender Female, n (%) Male, n (%)	 20 (69.0) 9 (31.0)	 9 (69.2) 4 (30.8)	1.000
Atopy, n (%)	6 (25.0)	5 (41.7)	0.446
NSAID hypersensitivity duration, months median (min-max)	18 (1-180)	18 (2-180)	0.643
NSAID reaction number 2 ≥3	 7 (24.1) 22 (75.9)	 4 (30.8) 9 (69.2)	0.713
NSAID reaction severity Grade 1 Grade 2 Grade 3 Grade 4	 8 (27.6) 12 (41.4) 9 (31.0)	 4 (30.8) 3 (23.1) 6 (46.2)	
Non-allergic comorbidity, n (%)	12 (41.4)	4 (30.8)	0.733
Allergic comorbidity, n (%)	27 (93.1)	12 (92.3)	1.000
Asthma, n (%)	13 (44.8)	9 (69.2)	0.143
Nasal polyp, n (%)	10 (34.5)	6 (46.2)	0.510
Asthma and nasal polyp, n (%)	9 (31.0)	6 (46.2)	0.488
Other drug allergy	11 (37.9)	2 (15.4)	0.278
Chronic urticaria / angioedema	5 (17.2)	2 (15.4)	1,000
Allergic rhinitis	4 (13.8)	3 (23.1)	0.657
Non-allergic rhinitiis	1 (3.4)	1 (7.7)	0.528
Venom allergy	1 (3.4)	1 (7.7)	0.528
Food allergy	0 (0.0)	0 (0.0)	1.000
Asthma duration,months median(min-max)	60 (0-240)	24 (0-60)	0.164
Nasal polyp duration,months, median(min-max)	36 (0-240)	12 (0-36)	0.108
Presence of polyp operation n (%)	7 (70.0)	2 (33.3)	0.302
Polyp operation number median(min-max)	2 (1-3)	2 (2-2)	0.857
Asthma and nasal polyp coexistence Respiratory symptoms, n (%) Systemic symptoms, n (%)	 4 (44.4) 5 (55.6)	 3 (50.0) 3 (50.0)	1.000
Underlying chronic urticaria Urticarial exacerbation, n (%) Systemic symptoms, n (%)	 3 (60.0) 2 (40.0)	 2 (100.0) 0 (0.0)	1.000

NSAID: Nonsteroidal anti-inflammatory drug

Previous studies evaluating the safety of nimesulide and meloxicam in cross-reactive NSAID hypersensitivity reported variable reaction rates. In studies conducted with a total provocative dose of 100 mg nimesulide reaction rates between 8.1% and 21.2% were reported.[9-12] On the other hand different reaction rates were reported in studies conducted with different provocative doses of meloxicam; reaction rates have been reported between 4.76% and 16.4% with a total provocative dose of 7.5 mg, and between 3.92% and 14.3% with a provocative dose of 15 mg.[9-15] Considering studies conducted with higher doses of meloxicam Inomata et al.[16] reported a reaction rate of 33% (2 of 6 patients) with a provocative dose of 18.5 mg meloxicam in patients with multiple NIUA. Quinones Estevez et al.[17] reported provocation test positivity in all of 8 patients with cross-reactive NSAID hypersensitivity after a provocative dose of 22.5 mg meloxicam and noted that COX-2 selectivity decreased with increasing doses.

Although there are publications in the literature reporting that meloxicam is safer than nimesulide in cross-reactive hypersensitivity, no statistical difference was found in our study.[12]

In our study 42 of the patients whose alternative drug provocation tests were positive were challenged with both nimesulide and meloxicam and 13 of them (31%) reacted to both drugs. Similarly in a study including patients with cross-reactive NSAID hypersensitivity reported that 6 of 19 (31.6%) patients had reactions with both drugs.[12] In another study that included only patients with NERD, reactions to both drugs were reported in 7 out of 8 (88%) patients and they also stated that the rate of reactions with nimesulide, meloxicam and paracetamol was higher in NERD patient group compared to some studies in the literature.[9]

NERD is defined as a chronic eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps, which symptoms are exacerbated by NSAIDs, including aspirin. Clinical reaction is typically manifested by upper and/or lower respiratory symptoms.[18] In our study 106 patients had coexistence of asthma and nasal polyps. We observed that 45.6% of these patients developed systemic symptoms in addition to respiratory symptoms after NSAID intake and median number of previous nasal polyp surgeries was higher in patients accompanied by systemic response. We also observed that 33.3% of the NECD patients had systemic symptoms in addition to cutaneous symptoms after NSAID intake and allergic rhinitis was more common in patients describing systemic symptoms.

It is known that NSAID hypersensitivity is higher in asthma and nasal polyp patients than in the general population.[18] In this study we showed that partial selective COX-2 hypersensitivity is also significantly higher in patients with asthma and/or nasal polyp than other group of cross-reactive NSAID hypersensitive patients. We also showed that partial selective COX-2 hypersensitivity were significantly more common in the group of patients with a shorter duration of NSAID hypersensitivity.

Previous studies examining risk factors for reactions to alternative NSAIDs have reported different results. Pastorello et al.[19] reported that atopy and reaction to antimicrobial drugs increase the likelihood of intolerance of nimesulide and acetaminophen. However in their study the frequency of cross-reactive NSAID hypersensitivity in the patient group was not specified. Tepetam et al.[20] reported that the presence of atopy and reaction to antimicrobial drugs did not seem to influence the reactions to nimesulide in a patient group consisting of 37.9% of the patients described intolerance to multiple analgesics. Asero et al.[21] aimed to detect risk factors for intolerance to alternative drugs such as acetaminophen and nimesulide in different groups of patients with a history of adverse skin reactions (urticaria/angioedema, or anaphylaxis) after the ingestion of aspirin and other NSAIDs in their study. Sixty-nine of the 256 patients had underlying chronic urticaria. They reported that history of anaphylactoid reactions induced by NSAID represented a risk factor for urticaria after the ingestion of the alternative study drugs and atopic status was associated with a higher risk of reactivity to nimesulide. However history of intolerance to antibacterial drugs was not found to be associated with a higher prevalence of reactivity against acetaminophen and/or nimesulide. Terzioğlu et al.[11] reported that the anaphylaxis due to NSAID intake was a risk factor for intolerance to paracetamol and partial selective COX-2 inhibitors in a cross-reactive patient group.

In our study, we did not detect any difference between the groups in terms of reaction development with nimesulide and/or meloxicam in terms of atopy, NSAID grade, previous drug allergy, and underlying diseases other than asthma and/or nasal polyp.

In this study we observed that the time between the first NSAID hypersensitivity reaction and application allergy clinic was quite long (median 36 months), and that other accompanying drug allergies were at a significant level of 29.3%. These results suggest the necessity of public education about drug allergies.

Limitations

However, there were several limitations of this study. First limitation is the retrospective design of the study. Second limitation is the aspirin provocation test was not performed on all patients to confirm cross-reactivity.

CONCLUSION

The partial selective COX-2 inhibitors nimesulide and meloxicam are well tolerated alternatives in patients with cross-reactive NSAID hypersensitivity. Hypersensitivity to these drugs is significantly higher in patients with asthma and/or nasal polyp than other group of cross-reactive NSAID hypersensitive patients and also in patients with a shorter duration of NSAID hypersensitivity. Although they are highly tolerable drugs they can also cause grade 3 severe reactions so drug provocation tests should be carried out under supervision.

Abbreviations

ASA: Asetyl salicylic acid, COX: Cyclooxygenase (COX), DHR: Drug hypersensitivity reaction, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capasity, NECD: NSAIDs-exacerbated cutaneous disease, NERD: NSAIDs-exacerbated respiratory disease, NIUA: NSAIDs-induced urticaria/angioedema, NSAID: Nonsteroidal anti-inflammatory drug, PFT: Pulmonary Function Test, SPT: Skin prick test

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.10.2021, Decision No: 2012-KAEK-15/2373).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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